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In this episode, Taren Grom, Editor-in-Chief of PharmaVOICE Magazine, meets with Andrea Itano, Ph.D., Senior VP, Head of Research, Evelo Biosciences.

Taren: Dr. Itano, welcome to the WoW podcast program.

Dr. Itano: Thank you so much for having me on the podcast. I'm really looking forward to our discussion.

Taren: Me too. You are working in one of the hottest fields right now – autoimmune and inflammatory diseases. Tell me about what drew you to the scientific field and why this area is of such interest to you.

Dr. Itano: Yes, absolutely. Immunology is fascinating to me. The idea that too much of a good thing can be bad is played out really clearly in immunity and inflammation. So figuring out how to harness immune processes to do what we want therapeutically is, I think, one of the most intriguing scientific question that there is right now.

My first exposure to the field was from my first job in college and I actually got my undergraduate degree in botany, but then I happen to find a job with a neuroscientist because actually, I had to find a job and I couldn't find one in botany, so I found one with a neuroscientist studying inflammation in the brain caused by Lyme disease, and I was completely new to the whole field of human disease, and I was really struck by the observation that inflammation in one area of the body could have much broader systemic effects.

So when I went back to get my Ph.D. I chose immunology so that I could get a better understanding of the underlying causes of inflammatory diseases. And since that time we've learned so much more about the critical role that inflammation plays in many diseases like neurodegenerative and metabolic diseases, which hadn't initially even been thought of as inflammatory diseases. So it's really exploded as an area to explore therapeutically and it feels like we're right now on the cusp of being able to really understand how to control inflammation and to induce immune resolution in a safe way and I have found that Evelo, the company I'm at now made a great match for my interest in exploring how the immune system can be regulated locally for broader effects. So it kind of brought it back full circle for me.

Taren: Well, let's jump to that. Let's talk about how your research at Evelo is going and I know that you were in charge of leading the discovery and early clinical development of three novel

microbiotherapeutics. What was this experience like and what are you looking to do with those therapeutics in terms of the human body?

Dr. Itano: It's only been four years since I joined Evelo – less than four years – and it's been pretty amazing. I think what strikes me most when looking back is how quickly we moved, because during that time we identified the first therapeutic candidates. We got them into the clinic and we've even now had our first positive clinical results in psoriasis and atopic dermatitis, and that happened in such a short span of time. It's been like a dream actually come true for me.

The thing I find really rewarding from the research side is that it usually takes years and years to find out if something that you're exploring pre-clinically is going to actually work in the clinic on humans, so just to be able to translate the pre-clinical work into the clinic firsthand has been a really unique opportunity. And as you mentioned the story of the science behind it all has been really intriguing.

Taren: Why do you think you all were able to move so quickly from the pre-clinic to the clinic? As you said, it takes usually much longer than that.

Dr. Itano: Yes. So it's the platform really, the fact that we're using single strains of commensal bacteria that have been isolated from the human small intestine. So we have a library of these microbial strains and the microbes is the medicine. So as opposed to small molecule development or even antibodies where you have to get a hit and then you take that molecule forward and you manipulate it into a more potent or a more effective drug that you can then take into the clinic – our microbe is the drug. What we have to do is figure out how to manufacture it in a way that we'll be able to scale it up and it will retain its efficacy and its potency and we'll be able to get it to a level that we can administer it to patients. So that's one thing. We don't have five years of lead out in that sense. We just start with the medicine itself.

The second thing is that because these microbes are commensal bacteria and they're not engineered, we don't need to do a large pre-clinical toxicology package. We've gotten permission from the regulators to put together our pre-clinical sort of a limited pre-clinical tox package and then explore the safety in humans. So that's cut out I don't know how many years, five, seven years of work when you start from the initial hit to get into the patient.

Taren: Fascinating. That's really exciting and in addition to the psoriasis, you're also working on several other difficult to treat diseases for patients. Can you talk a little bit more about the pipeline?

Dr. Itano: Yes. If I back up a moment – the microbes because they're working through the small intestine to impact peripheral diseases, this is a really, this is actually – I mean it's the fundamental concept of our microbes, and it's also a really I think something that was fairly non-obvious that we've worked through from the very beginning. We started with the observation made at the Mayo Clinic that an orally administered single strain of commensal bacteria could inhibit inflammation not just in the gut, but in other parts of the body as well. So in a mouse

model of arthritis the strength could inhibit joint inflammation, and in a model of multiple sclerosis the same strain could inhibit inflammation in the spinal cord and prevent loss of limb function, and in skin inflammation models the same thing happens.

So we saw all of these things happening just from a locally contained microbe in the gut which was having an effect on the periphery. So these were really exciting observations. Also, many closely related strains don't do the same thing. So the question was what was it about this particular strain that was allowing us to see these effects. And at the same time there was a lot of progress being made in the academic community around linking the effects in the gut with other parts of the body. I think if you're familiar with this area these links are now being called the gut-brain access or the gut-lung access or the gut-liver access, and it's basically showing that the small intestine is connected to the rest of the body via multiple distributed systems like the immune system, the nervous system and the metabolic system and that different diseases that's happening in the gut can affect what is happening elsewhere in the body.

So it made sense that the bacteria that we were studying and that we knew were restricted to the gut might be using those links to effect peripheral inflammation. Since then, we've made a lot of progress in understanding how the local interactions in the gut can link to systemic significant effects on distal immune responses in the skin, for example. So then that leads us back to our initial clinical trials in psoriasis, and more recently we've gotten data from atopic dermatitis, but of course we're not just looking at skin; we're going to be looking at other body processes. We have some pre-clinical programs that I'm not going to talk about right now, but we're interested in other areas like neuroinflammation and metabolic diseases and we also have an oncology candidate.

Taren: Really fascinating. Do you see this as the future of medical research? I mean it sounds like you have hit upon some really groundbreaking thinking in terms of how to control so many diseases just through the gut.

Dr. Itano: We're working with microbes now, but really the point of what we're doing is to show that there's a connectivity between the small intestine and the rest of the body and we call that SINTAX, that's what we've coined it as, so small intestinal axis. So we are initially using microbes to harness that biology. There could be other things that come down the road, other types of molecules that might do the same thing. So I do feel like we're on the cusp as I said of a new type of immune control where you don't have to have a systemic drug to have an effect on part of the body where that drug itself might have additional pharmacology that you don't want or off-target effects. This is why we think that control through SINTAX is going to be so safe and yet effective at the same time and actually that's playing out right now in the clinic.

Taren: Fascinating and obviously you can only talk about so much of this, but it's really, really exciting to hear what the future might hold. So thank you for sharing all of that information with us. At the same time even though you had great success in moving so quickly from pre-clinic to clinic, we all know that R&D is fraught with any number of pitfalls that can deter or derail a program; and keeping scientists – especially young scientists up and coming – inspired and motivated is challenging. And you are a team leader working with more than a dozen

immunologists and chemists working on discovering the evolving therapies. How do you keep your team inspired and how do you then overcome some of the challenges that naturally occur when developing new drugs?

Dr. Itano: That's a great question. We think about that all the time because as you say, there are so many challenges to making a medicine and how do you stay resilient and I think a lot of it is about finding your own personal meaning in the process. So we all come to this for different reasons. It could be very personal. It could be from the science side. It can be from other interest that we have and so I think you really have to focus on what it is that brought you to the field or to the particular company or area of exploration and keep focusing on that and I think really the answer to that question broadly was in what you said, we're striving to make medicines that are accessible and affordable to patients around the world and that is an inspiring vision.

So how do we keep that vision alive for people on a day-to-day basis or a week-to-week basis? And one thing I really like about working at Evelo is that we are still small enough that scientists working in the discovery and research end of things can see the whole process from discovery to clinical development. So they do pre-clinical experiments that actually inform our clinical strategy and they get to see this. They get to experience this and every person in the company can feel that they have an impact, a direct impact on the development of our medicines and then of course ultimately on patients' lives.

So I would say that our commitment to patients is ultimately what inspires the team to keep striving and when I think about this, when it comes down to it we're basically just a bunch of people who really believe in what we do and we don't want to run anyone down. We don't want to let each other down and we don't want to let the patients down.

Taren: I love that. And I think that is a very unusual place to be too, because if you look at the larger pharma companies or biopharma companies or biotech companies they don't always have that privilege of seeing it as you said from pre-clinical to clinical because it gets handed off. So you really do have the unique opportunity there.

Dr. Itano: Yes Taren. Actually, it's funny because I tell people that I tell the genius scientists in my group you don't know what an opportunity this is to be able to see all of this going through because exactly as you said it gets handed off. You work on something for 10 years and then it goes someplace else and maybe later on you'll hear about it. But this is a place where we've got people from process development and manufacturing sitting in on our research meetings because we move so quickly that they need to know what's coming down the pipeline for them makes our working on things, we're doing pre-clinical studies that are impacting the process all the way along and it's I think, I hope that that's very rewarding for the people in my group.

Taren: It's awesome. Talk to me about mentoring. I know that that's very important to you and in guiding that next generation of up and coming scientists. Why is this of particular interest to you?

Dr. Itano: Well, I think it's because I've always said that mentorship is one of the most important ways that we basically invest in our future, so it should be a large part of training the next generation of scientists and we have to do that. That is our responsibility. It takes years and years of accumulated experiences to learn what we know, so for those of us who are a bit older hopefully we know a bit more than those who are just starting out their journey. So if we want to make real progress, we have responsibility to teach what we've learned to those who are starting out on their own. As an example, my own experiences with mentors probably changed the course of my life and my career certainly.

As an undergrad, I worked as a lab assistant washing glassware and autoclaving pipettes and cleaning equipment and the head of the lab I was working in who also happened to be head of the department, so here's a pretty big guy, actually took a lot of time to teach me the basics, so how to use micropipette, how to pour a gel and run a gel and how to use dialysis tubing – I mean all of these really, really basic things, and he was kind and patient and along the way he instilled the concept of good scientific principles. And at the time I thought wow, this is amazing, but now I realize that he was making an intentional investment in me and he thought as a responsibility and it was because of him that I eventually got my Ph.D. and developed a career in science.

So I know that I benefited from the advice and perspective of the mentors – the many mentors – over my career and I feel very grateful for them. So now I feel the same responsibility to invest in my team.

Taren: That's excellent. Do you have any particular tips that you can share that make for a successful mentoring relationship, things that you might have learned along the way? That personal investment is certainly part of it.

Dr. Itano: Yeah, absolutely. There's so many things it's hard to sort of put them all together, but I think one of the things that I find so gratifying and I think it's really important is understanding that mentorship is often basically about helping someone figure out what the meaningful questions are that they need to be answering. So with many scientists, many young scientists especially, there's so many questions, so many things that they want to understand. There's so many things we can do and there's so many ways, technical ways and also fairly complex ways that we can answer questions and we want to do everything.

And so as a mentor, I think one of the things that you can do for somebody is to really help them to understand what are the meaningful questions. What's important for moving a program forward to get to an answer or ultimately to make a medicine that patients want and that they need? So it's very gratifying when you can help somebody develop that sense, that mindset that allows them to ask themselves what is the key question or the thing that will lead to an important decision. And then of course when they start applying that and they run up against a challenge and they work through it and they find a solution and they're excited about it, it's great as a mentor to be able to share in their excitement. It's a really great moment.

Taren: That's awesome. Over the last four years, can you identify one or two of the most rewarding aspects of leading your research teams? What had been a couple of high points for you?

Dr. Itano: Yeah. There had been so many, so many things. The people of course, just on a very basic level getting to know people and again to go back to a previous thing, these are young really enthusiastic scientists and so getting to sort of experience the learning process especially around drug development, seeing it through their eyes and watching them grow and develop and also seeing their dedication in working hard, working in a new area, working out the science behind a novel therapeutic approach has probably been one of the most rewarding aspects is having this great group of people of scientists with kind of the unknown science and putting all of their skills together, working together and putting forward hypothesis and carrying out the experiments, getting the answers and then moving forward and then now putting together sort of this foundational biology for us. And now this biology it feels like we all accept it and this is basis of our therapeutics. But when we started out this was not at all obvious that this was true or that it would work. So having it play all the way through from basic research to clinical results has been really amazing.

Taren: That is amazing. That's awesome. How would you describe yourself as a leader? How would your team describe you as a leader?

Dr. Itano: That's a good question. The way I see myself as a leader is I think that everybody has their great skills, their capability. Everyone has at least one thing that they're really awesome at and everybody has something that they need to develop. And I see my job is to really set the course and the direction of where we're going with our research to ask the questions that prompts people to do the right experiments, to connect us – to connect my group with the executive teams so that they have an understanding of the strategy of the company and why we're doing what we're doing so that they can feel that they are empowered to do what they need to do to support the goals of the company and part of that is also – I'm fairly hands off and that might be good for some people and maybe it's not good for others, but I have to say I definitely not a micromanager.

So what I do like to do is get people to understand what it is that they should be doing, that they can be doing and then let them kind of go off and do it and explore it and then come back for guidance or come back for feedback. But I really like people to go off and learn on their own and explore.

Taren: Excellent. Right now, we're living in some unprecedented times. How is the pandemic impacted your teams and how you lead them? Has it been an appreciable difference?

Dr. Itano: Now that's a really good question because so many things happened as a result of the pandemic, but one thing that I think we have an advantage during this time is that our group is primarily had been together for over the last three years. So we all know each other really, really well. So when we had to kind of step back and think about reducing the number of scientists to go into the lab or setting up more Zoom meetings or team meetings and how we're

going to communicate results and how we're going to have really good scientific discussion, it helps a lot that we already knew and understood each other's personalities. Some things have emerged. I think we've all learned more about ourselves and our own levels of resilience, but during this time we in some ways I think we have more discussions than we used to before because we kind of have these open channels now where rather than saying oh, can I find somebody and they happen to be in the lab and I'll wait to talk to them.

Now, everyone is on media. Everyone is on Teams. Everyone is checking their phone all the time for good or bad and so when you send out a question, when you message a question they come back almost immediately now. It's never happened before. So for me it's been great and it's also kind of fun where you can have a team chat and we put forward a question and literally in two minutes you see three people starting to respond and everyone is sort of piling in, so that's something that we actually didn't have before and I would really like to continue that after we normalize after we all do go back to the lab, which hopefully will be soon.

Taren: Yeah. I asked that question because always looking for those silver linings out of such great tragedy that everybody has experienced over the last year. So that's a great silver lining, so thanks for sharing that. Just to change tacks just a little bit, I know you're also involved in a number of different nonprofit organizations such as Global Arts Live and P-A-T-H (or PATH). Tell me a little bit about these groups and why these are important to you. You're a very busy person. I can imagine that you have a lot of balls in the air all the time, so to devote some part of your life and your resources to these organizations I'm curious.

Dr. Itano: Yeah, thanks Taren. You're right. It is very important to me and my husband and I have chosen to be involved in the two organizations you mentioned Global Arts Live and PATH, and I think the reason simply is that even though we're busy I think it's important that we make time in our lives to support particularly nonprofit organizations to go out and try to make – to try to have a broader impact on society as a whole and so we all have to do our part. This is the way we do ours and the way to do it I think is to find something that resonates with you in your personal mission perhaps or the things that you're trying to achieve in life.

So for example, PATH is a global health organization. It's headquartered in Seattle and its mission is to work with countries to develop new technologies to help address health issues like infectious diseases and maternal fetal nutrition, women's health issues and what I really like about them is that they focus on health equity and using technology and innovative approaches to expand access to healthcare for people who really has very little access to healthcare.

Taren: I love that health equity because it's such a – it's so important right now. The pandemic has shown such a bright spotlight on where there are so many areas of inequity in our healthcare system around the globe.

Dr. Itano: Yes, yes, no you're actually right. It's interesting because PATH in general has focused around maybe emerging countries that really have even really, really poor healthcare infrastructure, but you're right. The pandemic has shown that even in a country like the United States it's really not equitable in many cases and the pandemic has revealed that to us. So I

think actually something like PATH, which it's not just working overseas. I mean they have a lot of initiatives in the United States as well and so I think it's the time for something like that for an organization like that to be spotlighted.

Taren: So now tell me about Global Arts Live.

Dr. Itano: So Global Arts Live on the other hand, different from PATH it's actually a really small local organization that operates out of Cambridge, Massachusetts and the mission is to bring world music and dance performances to the Boston area. And when we moved to the Boston area, my husband and I, we really enjoy music and so we started going to a lot of these concerts and performances put on by Global Arts Live and we thought wow, this is a really great little company and so we wanted to get more involved in it and support it. It's so small. It's not the Boston Ballet. It's not the Boston symphony orchestra. They have about six people that run this group and they've been doing it for over 20 years and I think it's really important to support a small group as well as the larger ones.

And so although these PATH and Global Arts Live seem on the surface like they're unrelated, what ties them and resonates for me, what ties them together is that they both provide connections between us and the rest of the world. And I feel that a lot of issues in the world and even in our country arise from xenophobia, so this fear of things that we don't understand and the fear drives pretty bad behavior and outcomes for everybody. So it's important to support groups that try to open up our understanding of our cultures to something like music and dance, which is pretty nonpolitical. So of the things in the world that I think you think that people can relate across all spectrums, all political spectrums is music and PATH for some reason or pet ownership, but I'm focusing on music right now and also to help equity initiatives that allows to better understand what patients in other countries has to deal with. So those are the two things that's the underlying theme that resonates for me and that's why we support both of these groups.

Taren: It's such a wonderfully profound feeling there that you're looking for that connection that unites us on a most basic level and it's music, dance and health. I mean it has no political affiliation and such as the virus. It doesn't know who you are. It doesn't care who you are. So well thank you for sharing those stories and why these organizations are so important to you and it really is quite inspiring and it gives me hope for the future that there are so many people out there like you who are willing to invest their time and energy to move the world forward, so thank you. So we ask this of all of our podcastees and I'm going to ask you, put you on the spot, can you tell me about an accomplishment or wow moment that either shaped your career or changed the trajectory of your career? And I know you're going to say there's a quite a few of them, but I'm going to ask you to narrow it down to one if you wouldn't mind.

Dr. Itano: Sure, absolutely. I did think about this for awhile and I did manage to whittle it down to one that I would like to share. I talked a little bit about this earlier, but for me it was probably taking the leap from working in larger companies into a small biotech. Evelo Biosciences is small, and when I started there were only 36 people and not only was it a small company, my first small company, but it had a novel platform and as I described earlier, very novel science –

essentially unproven science. So it was a pretty big leap for me, and I was both a little scared (or maybe more than a little scared), but also really excited to take the risk. It felt like it was the time for me to make that jump and it was a real change and I would say for me it was a real change for the better.

I saw how quickly we could move when everybody passionately shared the same vision and put all their will and energy behind a single goal and the way I describe it often is like being part of a laser beam, how people talk about being in the zone or the flow and that's kind of how it feels. We're all in the same boat and we're rowing in the same direction to use that metaphor and I got a real sense of how much a small group of people can do when they're committed and when – and actually when they like each other, that's the other thing. There's a real camaraderie. Everyone has a reasonably good sense of humor about things and I think we work together really well.

So ultimately that made me see myself differently. It made me realize that I could do more than I had thought I could before because here we were such a small group of people and we were just moving this forward and ultimately if things continue to play out we will develop medicines for patients with important unmet need and we'll get there very quickly hopefully and that's something that for me, I wouldn't say exactly it was a bucket list item, but it something that is really like a dream.

Taren: That's awesome. Thank you so much for sharing and you know as the saying goes, there's nothing that a small committed group of people can't do. So I want to thank you so much Dr. Itano for spending some time with us, for sharing your really inspirational story and for shedding some light on a little groundbreaking technology that we'll be looking forward to seeing what's going to come in the future. I think the developments are going to be quite extraordinary if everything plays out and you're really on the cusp of something big here. So thank you so much for being with us and thank you so much for sharing your thoughts with us today.

Dr. Itano: Oh, thank you Taren. It's been a real pleasure.

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